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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,747	09/24/2003	Peter Martin Fischer	CCI-027CN	9353

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/671,747	FISCHER ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *31104*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating lung cancer, does not reasonably provide enablement for treatment of all types of diseases of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims are drawn to "a method of treating a proliferative disorder" which include cancers, leukemias, etc. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedures for CDK inhibitory activity is provided using CDK2/cyclin E in the specification Example 17 and the CDK inhibitory activity data (in terms of IC_{50}) for some of the compounds of the invention is provided in Table 1. Further, the specification provides Example 18 showing anti-proliferative effect for some of the compounds using human tumor cell lines, e.g., A549 which is a lung cancer cell line and the corresponding results in Table 2. However, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the entire scope of the disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders or cancers which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the

claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Regarding CDK mechanism, Blain et al. (J. of Biol. Chem.) report that "their specific functions are still poorly understood" (see page 25863, col. 1). Also, LuValle et al. (Frontiers in Bioscience) express that "detailed analyses of these pathways are necessary for a complete understanding of chondrocyte proliferation and differentiation" (see page 5, section 4). This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of

cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. The second proviso statement in claim 1 is not clear. It is recited "with the proviso that when R^1 and R^2 ....., the phenyl group is not unsubstituted, 4-ethyl, 3-methyl.... When the other groups R^4-R^8 are H". It is not clear what the terms '4-ethyl, 3-methyl, ...' are intended for. It appears that there is some phrase missing before '4-ethyl, 3-methyl...'.
2. In claim 1, it is recited that "A compound.... **and** the pharmaceutically acceptable salts thereof", which is unclear because it is not clear if 'a compound or a salt thereof' is claimed **or** 'a **mixture** of a compound and the salt' is claimed. Replacing with -- A compound..... ~~and the~~ or a pharmaceutically acceptable ~~salts~~ salt thereof -- would overcome the rejection.
3. Regarding claim 21, the phrase "preferably" (see line 2) renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. Similar recitation also appears in other claims, see e.g., claim 22, line 3.
4. Claims 30-34 provide for the use of the compounds, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

Claims 30-34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1, 3-5, 9-11 and 28-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Torley et al., EP 233461. The instant claims read on reference disclosed compounds, see e.g., the compound disclosed in Table 1, page 8, first compound; page 11, second compound. Applicant's attention is directed to the CAPLUS abstract of EP 233461 (Abstract No. 108:112478) and the compound RN 112722-32-4.

2. Claims 1, 3-4 and 29-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Kois et al., U.S. Patent Application Publication No. 2003/0203926 (effective filing date December 6,

2000). The instant claims read on reference disclosed compound, see the compound 3-7 in page 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 9-11 and 28-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torley et al., EP 233461. The reference teaches pyrimidinyl compounds, see formula in page 2, and the corresponding compounds in Tables. The reference compounds are taught to be useful –pharmaceutical therapeutic agents, see the abstract. The instant claims exclude some of the reference disclosed compounds, see the proviso statement, however, include compounds that differ by a $-CH_2$ group, i.e., wherein any of the groups are substituted by a methyl. For example, the instant claims exclude the reference disclosed compound of N-(4-ethylphenyl)-4-(1H-pyrrol-

2-yl)-2-pyrimidinamine, however, include compounds wherein the phenyl is substituted with a 4-methyl or 4-propyl group or the pyrrole is substituted with a methyl group, etc. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and it is well established that compounds that differ by a $-CH_2$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Claims 1-2 and 29-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al., U.S. Patent Application Publication No. 2003/0092714 (effective filing date February 9, 2001). The reference teaches compounds of pyrimidyl compounds, see formula III' in page 10 wherein the Sp is a (pyrrole) and further, the compound 1 (page 17) and compound 119 (page 27) in Table 1^A. The compounds have the $-T_mR^1$ group attached to the 5-position of the pyrimidine. The instantly claimed compounds on the other hand, have R^3 at the 6-position. The reference compounds are taught to possess protein kinase inhibitory activity, see the abstract. Since the instantly claimed compounds differ only by the position of the substituents, they are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are isomers of the reference compounds. One having ordinary skill in the art would

have been motivated to prepare the instantly claimed compounds because such structurally isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds. It has been held that a compound which is isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950). *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

***Note**: Applicant cannot rely upon the foreign priority papers to overcome this rejection because a certified copy of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.*

Allowable Subject Matter

Claims 6-8 and 12-27 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on March 11, 2004 and a copy is enclosed herewith.

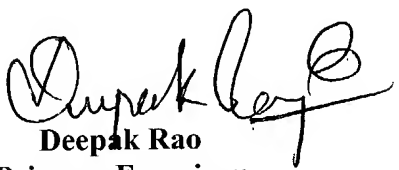
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

June 24, 2004